Efficacy of implantable haemodynamic monitoring in heart failure across ranges of ejection fraction: a systematic review and meta-analysis

James P Curtain, Matthew M Y Lee, John JV McMurray, Roy S Gardner, Mark C Petrie, Pardeep S Jhund

ABSTRACT

Aims We conducted a meta-analysis of randomised controlled trials (RCTs) of implantable haemodynamic monitoring (IHM)-guided care.

Methods PubMed and Ovid MEDLINE were searched for RCTs of IHM in patients with heart failure (HF). Outcomes were examined in total (first and recurrent) event analyses.

Results Five trials comparing IHM-guided care with standard care alone were identified and included 2710 patients across ejection fraction (EF) ranges. Data were available for 628 patients (23.2%) with heart failure with preserved ejection fraction (HFpEF) (EF ≥50%) and 2023 patients (74.6%) with heart failure with a reduced ejection fraction (HFrEF) (EF <50%). Chronicle, CardioMEMS and HeartPOD IHMs were used. In all patients, regardless of EF, IHM-guided care reduced total HF hospitalisations (HR 0.74, 95% CI 0.66 to 0.82) and total worsening HF events (HR 0.74, 95% CI 0.66 to 0.84). In patients with HFpEF, IHM-guided care reduced total worsening HF events (HR 0.75, 95% CI 0.66 to 0.86). The effect of IHM-guided care on total worsening HF events in patients with HFpEF was uncertain (fixed-effect model: HR 0.72, 95% CI 0.59 to 0.88; random-effects model: HR 0.60, 95% CI 0.32 to 1.14). IHM-guided care did not reduce mortality (HR 0.92, 95% CI 0.71 to 1.20). IHM-guided care reduced all-cause mortality and total worsening HF events (HR 0.80, 95% CI 0.72 to 0.88).

Conclusions In patients with HF across all EFs, IHM-guided care reduced total HF hospitalisations and worsening HF events. This benefit was consistent in patients with HFpEF but not consistent in HFpEF. Further trials with pre-specified analyses of patients with an EF of ≥50% are required.

PROSPERO registration number CRD42021253905.

INTRODUCTION

Remote monitoring using implanted devices may provide useful information about the natural history of congestion leading to decompensation in people with heart failure (HF). Early identification of increasing cardiopulmonary pressures and intervention to reduce these might decrease the risk of subsequent HF hospitalisation. Based on the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association Class III Heart Failure Patients (CHAMPION) trial, one implantable pulmonary artery pressure monitor (CardioMEMS, Abbott, Illinois, USA) received a class IIb recommendation to reduce HF hospitalisations in the 2021 European Society of Cardiology Heart Failure guidelines. In the Hemodynamic-Guided Management of Heart Failure (GUIDE-HF) trial, the largest randomised controlled trial (RCT) to compare implantable haemodynamic monitoring (IHM) with standard care, IHM-guided care did not reduce HF hospitalisations overall, but sensitivity analyses suggested a modest benefit before the COVID-19 pandemic had an impact on patient management.

No previous meta-analysis has included data from both the GUIDE-HF and the Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy (LAPTOP-HF) study, the latter of which was an international RCT that reported its findings in 2016 (table 1). Additionally, despite IHM randomised trials recruiting patients across a range of EFs, combining data from the five randomised trials that investigated IHM-guided treatment, including a pre-COVID-19 sensitivity analysis from the recent Hemodynamic-Guided Management of Heart Failure (GUIDE-HF) trial. This study demonstrates that IHM-guided treatment was effective at reducing worsening heart failure (HF) events in patients with an EF of <50%; it is uncertain if patients with HF with preserved EF receive the same benefit.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Implantable haemodynamic monitoring (IHM) to guide treatment has a class IIb recommendation in the 2021 European Society of Cardiology Heart Failure Guidelines.

WHAT THIS STUDY ADDS

⇒ This is the first meta-analysis to examine the effectiveness of IHM-guided care across a range of ejection fractions (EFs), combining data from the five randomised trials that investigated IHM-guided treatment, including a pre-COVID-19 sensitivity analysis from the recent Hemodynamic-Guided Management of Heart Failure (GUIDE-HF) trial. This study demonstrates that IHM-guided treatment was effective at reducing worsening heart failure (HF) events in patients with an EF of <50%; it is uncertain if patients with HF with preserved EF receive the same benefit.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study indicates that future trials should focus on people with an EF of ≥50% with pre-specified analyses to confirm the effectiveness of IHM-guided care in this population. IHM-guided treatment can be considered as a strategy in patients with an EF of <50%.
range of ejection fractions (EFs), no meta-analysis reported the effect of IHM on the reduction of HF hospitalisations and related events in subgroups of patients with HF with preserved ejection fraction (HFpEF) or heart failure with a reduced ejection fraction (HFrEF). This type of monitoring is of particular interest in patients with HFpEF, in whom evidence-based

### Table 1  Randomised controlled trials of IHM-guided HF management compared with standard care

<table>
<thead>
<tr>
<th>Trial</th>
<th>First author and year</th>
<th>Design, country</th>
<th>Primary efficacy endpoint</th>
<th>Numbers enrolled</th>
<th>EF (%)</th>
<th>NYHA class (%)</th>
<th>Previous HF event (%)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPASS-HF</td>
<td>Bourge et al.19, 2008</td>
<td>Single-blind, *multicentre RCT; USA</td>
<td>HF hospitalisation and ED and urgent clinic visit for intravenous therapy (including hypovolaemic events)</td>
<td>274</td>
<td>No EF inclusion criterion III-IV</td>
<td>≤6 months (or ED visit)</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>CHAMPION</td>
<td>Abraham et al.,18 2011</td>
<td>Single-blind, *multicentre RCT; USA</td>
<td>HF hospitalisation</td>
<td>550</td>
<td>No EF inclusion criterion III</td>
<td>≤12 months</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>REDUCE-HF</td>
<td>Adamson et al.,10 2011</td>
<td>Single-blind, *multicentre RCT; USA</td>
<td>HF hospitalisation and ED and urgent clinic visit for intravenous therapy</td>
<td>400</td>
<td>No EF inclusion criterion II-III</td>
<td>≤12 months</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>LAPTOP-HF</td>
<td>Abraham et al.,17 2016</td>
<td>Multicentre RCT (no blinding); USA and New Zealand</td>
<td>HF hospitalisation and complications from HF therapy</td>
<td>486</td>
<td>No EF inclusion criterion III</td>
<td>≤12 months (or BNP ≥400 pg/mL or NT-proBNP ≥1500 pg/mL)</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>GUIDE-HF</td>
<td>Lindenfeld et al.,2 2021</td>
<td>Single-blind, *multicentre RCT; USA and Canada</td>
<td>All-cause mortality and HF hospitalisation and ED and urgent clinic visit for intravenous therapy</td>
<td>1000</td>
<td>No EF inclusion criterion II – IV</td>
<td>≤12 months (or BNP ≥250 pg/mL or NT-proBNP ≥1000 pg/mL)</td>
<td>12 months</td>
<td></td>
</tr>
</tbody>
</table>

*Patients but not investigators were blinded to haemodynamic data.

BNP, brain natriuretic peptide; CHAMPION, CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association Class III Heart Failure Patients; COMPASS-HF, Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure; ED, emergency department; EF, ejection fraction; GUIDE-HF, Hemodynamic-Guided Management of Heart Failure; HF, heart failure; IHM, implantable haemodynamic monitor; LAPTOP-HF, Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RCT, randomised controlled trial; REDUCE-HF, Reducing Events in Patients with Chronic Heart Failure.

### Table 2  Key baseline characteristics of patients enrolled in randomised controlled trials of IHM-guided HF management compared with standard care

<table>
<thead>
<tr>
<th>Trial</th>
<th>COMPASS-HF</th>
<th>CHAMPION</th>
<th>REDUCE-HF</th>
<th>LAPTOP-HF</th>
<th>GUIDE-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>IHM arm: 58±14 Control arm: 58±13</td>
<td>IHM arm: 61±13 Control arm: 62±13</td>
<td>IHM arm: 55±15 Control arm: 55±15</td>
<td>IHM and control arms: 62±12</td>
<td>IHM arm: 71 (64-76) Control arm: 70 (64-77)</td>
</tr>
<tr>
<td>Sex (male, %)</td>
<td>IHM arm: 66 Control arm: 64</td>
<td>IHM arm: 72 Control arm: 73</td>
<td>IHM arm: 70 Control arm: 67</td>
<td>IHM and control arms: 75</td>
<td>IHM arm: 62 Control arm: 63</td>
</tr>
<tr>
<td>EF (n=participants) ≥50%, 70 &lt;50%: 204</td>
<td>≥50%, 66 ≤40–49%, 53 ≤40%, 456 &lt;40%, 430</td>
<td>IHM and control arms: mean EF ≥2%±7</td>
<td>IHM and control arms, EF &gt;35%: 121</td>
<td>IHM and control arms, EF ≤35%: 365 Mean EF 30%±15</td>
<td>IHM arm: ≥50%: 321 ≤50%: 679</td>
</tr>
<tr>
<td>NYHA class (%)</td>
<td>IHM arm: All: 84</td>
<td>IHM arm: III only Control arm: III only</td>
<td>IHM arm: II: 53</td>
<td>IHM arm: III: only Control arm: III only</td>
<td>IHM arm: II: 29 III: 65 IV: 6</td>
</tr>
<tr>
<td>Ischaemic aetiology (%)</td>
<td>IHM arm: 47 Control arm: 44</td>
<td>IHM arm: 59 Control arm: 62</td>
<td>IHM arm: 45 Control arm: 44</td>
<td>IHM and control arms: 46</td>
<td>IHM arm: 42 Control arm: 38</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>IHM arm: 93 Control arm: 99</td>
<td>IHM arm: 92 Control arm: 92</td>
<td>IHM arm: 93 Control arm: 97</td>
<td>n/r</td>
<td>IHM arm: 95 Control arm: 95</td>
</tr>
<tr>
<td>ACEi/ARB (%)</td>
<td>IHM arm: 85 Control arm: 81</td>
<td>IHM arm: 76 Control arm: 79</td>
<td>IHM arm: 92 Control arm: 92</td>
<td>n/r</td>
<td>IHM arm*: 64 Control arm*: 64</td>
</tr>
<tr>
<td>Beta blockers (%)</td>
<td>IHM arm: 83 Control arm: 81</td>
<td>IHM arm: 90 Control arm: 91</td>
<td>IHM arm: 96 Control arm: 96</td>
<td>n/r</td>
<td>IHM arm: 89 Control arm: 88</td>
</tr>
</tbody>
</table>

*ARNI/ACEi/ARB.

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor blocker-nesiritide inhibitor; CHAMPION, CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association Class III Heart Failure Patients; COMPASS-HF, Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure; ED, emergency department; EF, ejection fraction; GUIDE-HF, Hemodynamic-Guided Management of Heart Failure; HF, heart failure; IHM, implantable haemodynamic monitoring; LAPTOP-HF, Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy; n/r, not reported; NYHA, New York Heart Association; REDUCE-HF, Reducing Events in Patients with Chronic Heart Failure.
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Figure 1  Total (first and recurrent) HF hospitalisations in all patients regardless of EF. CHAMPION, CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association Class III Heart Failure Patients; COMPASS-HF, Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure; D+L, DerSimonian and Laird; EF, ejection fraction; GUIDE-HF, Hemodynamic-Guided Management of Heart Failure; HF, heart failure; IHM, implantable haemodynamic monitor; I-V, inverse variance; LAPTOP-HF, Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy; REDUCE-HF, Reducing Events in Patients with Chronic Heart Failure.

treatment options are limited. Therefore, in this meta-analysis of all randomised trials using IHM, we investigated whether treatment guided by such monitoring reduced the risk of total (first and recurrent) HF hospitalisations, total worsening HF events (HF hospitalisation and emergency department (ED) and urgent clinic visit for intravenous HF therapy) and all-cause mortality, when compared with standard care, in patients with HF across a range of EFs.

METHODS
Search strategy and data extraction
A systematic review of RCTs in patients with HF was performed, comparing IHM-guided care versus standard therapy. This meta-analysis was registered on PROSPERO (CRD42021253905). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to conduct the literature search, data extraction and reporting. A PRISMA checklist is included in online supplemental appendix, table S1). Bias was assessed using the Revised Cochrane Risk-of-Bias Tool for Randomised Trials 1 (online supplemental appendix, table S2). Searches were performed on public databases (PubMed and Ovid MEDLINE) between 1 May 2020 and 5 September 2022 using the terms “heart failure AND implantable AND haemodynamic monitoring” and “left atrial pressure AND heart failure AND monitoring” and “pulmonary artery pressure monitoring AND heart failure”. All studies published up to 5 September 2022 were eligible. No restriction was placed on study size, language or country of publication. Titles and abstracts were screened based on pre-specified inclusion criteria using the population, intervention, comparator, outcomes and study framework:

- Population: patients with HF.
- Intervention: IHM-guided care.
- Comparator: standard care.
- Outcomes of interest.
  - HF hospitalisation.
  - Worsening HF events (HF hospitalisation and ED and urgent clinic visits for intravenous HF therapy).
  - All-cause mortality.
  - All-cause mortality and HF hospitalisation.
  - All-cause mortality and worsening HF events.
- Study design: RCTs.

Full-text articles of original trial reports and published articles with retrospective analyses of the RCTs were included. Data presented at conferences were included if the presentation was available and verifiable by the researchers. Hazard ratios (HRs) and incidence rate ratios (IRRs) for endpoints were recorded. IRRs are approximations of HRs and were included as the effect estimate if HRs were not available as has previously been reported.4–6 If either HR or IRR was not reported in the literature, the IRR was calculated using event numbers and study cohort time at risk. Ninety-five per cent CIs were calculated if only a p value and effect estimate were reported.7 Numbers of patients in EF subgroups and their numbers of events were calculated from available data where necessary. Two researchers (JPC and MMYL) independently extracted and analysed the data. Results were compared and differences resolved by consensus with opinion from a third author. All authors reviewed the analysis results and contributed to drafting the report. If data were not available, the original study authors were contacted and data were requested.
Systematic review

<table>
<thead>
<tr>
<th>IHM Guided</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/Patients</td>
<td>Events/Patients</td>
</tr>
<tr>
<td><strong>Trial</strong></td>
<td></td>
</tr>
<tr>
<td>COMPASS-HF - All EF%</td>
<td>84/134</td>
</tr>
<tr>
<td>CHAMPION - All EF%</td>
<td>182/270</td>
</tr>
<tr>
<td>REDUCE-HF - All EF%</td>
<td>91/202</td>
</tr>
<tr>
<td>LAPTOP-HF - All EF%</td>
<td>80/211</td>
</tr>
<tr>
<td>GUIDE-HF - All EF%</td>
<td>213/497</td>
</tr>
<tr>
<td>I-V Overall</td>
<td>(I-squared = 38.2%, p = 0.167)</td>
</tr>
<tr>
<td>D+L Overall</td>
<td></td>
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</tbody>
</table>

Statistical analysis

Statistical analyses were performed using Stata17. As the trials investigated three devices across different decades we used a random effects (DerSimonian and Laird (D+L)) model so that differences in the studies’ designs and cohorts would be accounted for within the analysis. We performed sensitivity analyses of each meta-analysis using fixed-effect models. Only the result of the fixed-effect model in patients with HFpEF is reported, as the other fixed-effect analyses were consistent with the reported random effect models. I² statistic for percentage heterogeneity was computed with corresponding p values. Forest plots graphically report the pooled effect size estimates, the degree of heterogeneity and the weighted contribution each study made to the analyses. All outcomes were examined in total events (first and recurrent) analyses.

Definitions of HFpEF and HFrEF

HFpEF was defined as HF with an EF of ≥50% in keeping with the 2021 European Society of Cardiology Heart Failure guidelines and the recently proposed universal definition of HF. HFrEF was defined as HF with an EF of <50%, with the inclusion of patients with heart failure with mildly reduced ejection fraction (HFmrEF, EF 41%–49%) as well as patients with an EF of ≤40%. There were insufficient data available to further subclassify the trials into a HFmrEF subgroup. Only Chronic HFpEF was examined in total events analyses. All outcomes were examined in total events (first and recurrent) analyses.

Recurrent events were analysed in a negative binomial regression model in COMPASS-HF and an Andersen-Gill model in CHAMPION, REDUCE-HF, LAPTOP-HF and GUIDE-HF. As these methods yield very similar results in simulations and trial datasets, they were used in the meta-analysis. Meta-analysis was performed for (1) total HF hospitalisations, (2) total worsening HF events (HF hospitalisation and ED visit and urgent clinic visit for intravenous HF therapy), (3) all-cause mortality, (4) all-cause mortality and total HF hospitalisations, and (5) all-cause mortality and total worsening HF events. Only hospitalisations for greater than 24 hours in REDUCE-HF were included in that trial had severely impaired systolic function with a mean (±SD) EF of 23%±7%. Patients from the REDUCE-HF trial were therefore included in the HFpEF (EF <50%) analysis. Similarly, patients from LAPTOP-HF, in whom the mean EF was 30%±15% were included in the HFpEF (EF <50%) analysis.

Efficacy endpoints

The primary efficacy endpoints for each of the included trials were examined in total (first and recurrent) event analyses comparing the effect of IHM-guided care with standard care alone. These endpoints were as follows:

- COMPASS-HF and REDUCE-HF: total worsening HF events. HF hospitalisations for less than 24 hours were included in the composite endpoint in REDUCE-HF.
- LAPTOP-HF: total HF hospitalisation and complications of HF treatment such as hypotension and acute renal failure.
- CHAMPION: total HF hospitalisation.
- GUIDE-HF: all-cause mortality and total worsening HF events.
in the total HF hospitalisation analysis (aforementioned item 1). All-cause mortality data from COMPASS-HF, CHAMPION, REDUCE-HF and GUIDE-HF were pooled. The GUIDE-HF main trial results were published in 2021, followed by an analysis examining the impact of the COVID-19 pandemic on that trial’s event rates.14 We performed a sensitivity analysis examining the rate of HF events including the pre-COVID event rates and the results from the other four included trials.

RESULTS

Literature review and search strategy
A total of 1373 articles were identified by searching electronic databases. Two further articles11 15 were found by hand searching references and internet searches. A PRISMA flow-chart outlines the search process and identification of relevant articles (online supplemental appendix, figure S1). Five RCTs were identified (table 1): COMPASS-HF,16 CHAMPION,17 18 REDUCE-HF,10 LAPTOP-HF11 15 and GUIDE-HF.2 The 18-month results for the CHAMPION trial were used in this meta-analysis. The HR for HF hospitalisation at 1 year was reported for 455 of the 486 randomised in LAPTOP-HF by the lead investigator at the annual meeting of the Heart Failure Association of the European Society of Cardiology in 2017.15

Trial characteristics
COMPASS-HF, CHAMPION and REDUCE-HF were conducted in the USA. LAPTOP-HF was conducted in the USA and New Zealand. GUIDE-HF was conducted in the USA and Canada. The COMPASS-HF and REDUCE-HF studies evaluated the Chronicle pressure sensor (Medtronic, Minnesota, USA). The CardioMEMS device (Abbott, Illinois, USA) was investigated in CHAMPION and GUIDE-HF. The HeartPOD device (St. Jude, Minnesota, USA) was investigated in LAPTOP-HF (table 1). The main trial characteristics are summarised in table 2.

All participants underwent implantation of haemodynamic monitors and were randomised to receive HF care guided by haemodynamic data or receive standard care. COMPASS-HF, CHAMPION, REDUCE-HF and GUIDE-HF were single-blind studies where investigators, but not patients, had access to the treatment group haemodynamic data. Patients were unaware of their randomised assignment groups in these four trials. LAPTOP-HF had no blinding (ie, patients and investigators were aware of the intervention assignment groups).

Patients with HF regardless of EF

Total HF hospitalisations
There were 591 hospitalisations in 1314 patients receiving IHM-guided care compared with 836 events in 1365 standard care patients. HF hospitalisations were reduced in the IHM-guided care arm by 26% (HR 0.74, 95% CI 0.64 to 0.85; low heterogeneity (I² 29.7%)) (figure 1).

Total worsening HF events
There were 650 composite outcome events in 1314 patients receiving IHM-guided care and 889 events in 1365 standard care patients. IHM-guided care reduced total worsening HF events by 26% (HR 0.75, 95% CI 0.63 to 0.88; low heterogeneity (I² 38.2%)) (figure 2). In a sensitivity analysis of pre-COVID-19 event rates in the GUIDE-HF trial, IHM-guided care reduced HF events by 29% (HR 0.71, 95% CI 0.63 to 0.81; low heterogeneity (I² 2.9%)).
### Discussion

The main results of this meta-analysis support the use of IHM in patients with symptomatic HF (irrespective of EF), demonstrating a 26% reduction in the risk of total worsening HF events, including hospital admission. This is the first meta-analysis to include total HF events from all IHM randomised trials, including LAPTOP-HF and the recently reported GUIDE-HF. We also report for the first time meta-analyses of the effectiveness of IHM-guided care in patients with HFrEF and HFpEF. The finding of a reduction in total worsening HF events in all patients regardless of EF was also present in patients with HFrEF, who comprised the majority of patients. The same benefit was not consistent in patients with HFpEF.
Patients with an EF of <50% have been shown to have higher resting intracardiac and pulmonary pressures than those with HFpEF, and in turn, patients with higher pressures are at greater risk of decompensation from even small rises in pressure.21–23 The relative reduction of total worsening HF events with IHM monitoring observed in this meta-analysis was comparable with the magnitude of benefit found in patients with HFpEF treated with an angiotensin receptor blocker-neprilysin inhibitor in the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial (sacubitril/valsartan reduced HF hospitalisations by 21% compared with enalapril) and the sodium glucose cotransporter 2 inhibitor dapagliflozin in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (PARADIGM-HF) trial (dapagliflozin reduced HF hospitalisations by 30% compared with placebo).24 25

Mortality data were not reported from LAPTOP-HF, and only 231 deaths were reported during the overall short average follow-up in the other four trials. With low numbers of deaths and limited follow-up periods, no IHM trial demonstrated a reduction in mortality with IHM-guided care. Accordingly, the 22% reduction in the composite endpoint all-cause mortality and HF hospitalisation with IHM-guided care observed in this analysis was driven by the favourable effect on hospitalisations. The rate of HF hospitalisations calculated for the standard care arms in individual trials in this analysis ranged from 42 per 100 patient-years in REDUCE-HF to an estimated 147 per 100 patient-years in COMPASS-HF. The reported rate of total HF hospitalisations in the standard care arm of GUIDE-HF, which investigated the only currently available IHM (CardioMEMS) in the most contemporary HF population, was 49.7 per 100 patient-years.2  This was markedly higher than the composite event rate for total HF hospitalisations and cardiovascular deaths in the placebo group of DAPA-HF (21.6 per 100 patient-years).26 The substantially higher hospitalisation rates in the IHM trials highlight two considerations. First, that patients in these trials were highly selected and prognostically vulnerable. Second, rates of hospitalisation will differ between the healthcare setting in which the IHM trials were conducted (USA predominantly) and that of other diverse settings of care as indicated by event rates in more international contemporary HF trials. The effectiveness, including cost-effectiveness, of such a targeted intervention as IHM and the system of care required to deliver it may accordingly differ, depending on the setting and is an important consideration for future IHM studies (online supplemental appendix, table S3).

To date, the main source of information on the effect of IHM in patients with HFpEF has been the CHAMPION trial. In that trial, the rate of HF hospitalisation was 41 events per 100 patient-years in the IHM arm compared with 139 events per 100 patient-years in the standard care arm, giving a 70% relative risk reduction in HF hospitalisation among patients with an EF of ≥50% when treatment was guided by IHM.19 Again, the rate of HF hospitalisation was substantially higher in CHAMPION than observed in other contemporary trials of patients with HFpEF. In PARAGON-HF, the rate of HF hospitalisation and cardiovascular death in the valsartan group was 14.6 per 100 patient-years.23 The reliability of the relative reduction for HF hospitalisation in patients with HFpEF reported in the CHAMPION trial is limited by the small number of patients (n=66) included in that analysis. Our new meta-analysis adds data on patients with HFpEF from COMPASS-HF and GUIDE-HF. With an additional 562 patients and 366 events, the fixed effect model demonstrated patients with HFpEF receiving IHM-guided

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**Figure 5** Total (first and recurrent) worsening HF events (HF hospitalisation and ED and urgent clinic visit for intravenous HF therapy) in patients with HFpEF (EF ≥50%). CHAMPION, CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association Class III Heart Failure Patients; COMPASS-HF, Chronic Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure; D+L, DerSimonian and Laird; ED, emergency department; EF, ejection fraction; GUIDE-HF, Hemodynamic-Guided Management of Heart Failure; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; IHM, implantable haemodynamic monitor; I-V, inverse variance; LAPTOP-HF, Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy; REDUCE-HF, Reducing Events in Patients with Chronic Heart Failure.

<table>
<thead>
<tr>
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<th>Guided Care Total</th>
<th>Standard Care Total</th>
<th>I-V</th>
<th>Value</th>
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<tbody>
<tr>
<td></td>
<td>Events/Patients</td>
<td>Events/Patients</td>
<td></td>
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<tr>
<td>COMPASS-HF - EFa50%</td>
<td>19/34</td>
<td>25/36</td>
<td>0.80 (0.54, 1.56)</td>
<td>13.46</td>
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<td>CHAMPION - EFa50%</td>
<td>13/35</td>
<td>31/31</td>
<td>0.30 (0.18, 0.48)</td>
<td>15.75</td>
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<tr>
<td>GUIDE-HF - EFa50%</td>
<td>154/not available</td>
<td>168/not available</td>
<td>0.86 (0.68, 1.08)</td>
<td>70.79</td>
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<td>I-V Overall</td>
<td>(I-squared = 86.4%, p = 0.001)</td>
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<tr>
<td>D+L Overall</td>
<td></td>
<td></td>
<td>0.72 (0.59, 0.88)</td>
<td>100.00</td>
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Systematic review

<table>
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<tr>
<th>IHM</th>
<th>Guided Care Total</th>
<th>Standard Care Total</th>
<th>HR (95% CI)</th>
<th>Weight</th>
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<tr>
<td>Trial</td>
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<td>Events/Patients</td>
<td>(I-V) Value</td>
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<tr>
<td>COMPASS-HF - EF&lt;50%</td>
<td>65/100</td>
<td>88/104</td>
<td>0.74 (0.53, 1.00)</td>
<td>15.31</td>
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<td>CHAMPION - EF&lt;40%</td>
<td>162/222</td>
<td>227/234</td>
<td>0.72 (0.59, 0.88)</td>
<td>42.28</td>
<td>0.001</td>
</tr>
<tr>
<td>REDUCE-HF - EF&lt;40%</td>
<td>91/202</td>
<td>90/198</td>
<td>0.99 (0.61, 1.61)</td>
<td>7.17</td>
<td>0.978</td>
</tr>
<tr>
<td>LAPTOP-HF - EF&lt;50%</td>
<td>80/211</td>
<td>155/244</td>
<td>0.57 (0.40, 0.80)</td>
<td>12.68</td>
<td>0.003</td>
</tr>
<tr>
<td>GUIDE-HF - EF&lt;40%</td>
<td>73/not available</td>
<td>96/not available</td>
<td>0.83 (0.61, 1.14)</td>
<td>17.28</td>
<td>0.260</td>
</tr>
<tr>
<td>I-V Overall</td>
<td>(I-squared = 6.7%, p = 0.374)</td>
<td></td>
<td>0.75 (0.66, 0.86)</td>
<td>100.00</td>
<td></td>
</tr>
<tr>
<td>D+L Overall</td>
<td></td>
<td></td>
<td>0.75 (0.66, 0.86)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 6  Total (first and recurrent) worsening HF events (HF hospitalisation and ED and urgent clinic visit for intravenous HF therapy) in patients with HFrEF (EF<50%). CHAMPION, CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association Class III Heart Failure Patients; COMPASS-HF, Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure; D+L, DerSimonian and Laird; ED, emergency department; EF, ejection fraction; GUIDE-HF, Hemodynamic-Guided Management of Heart Failure; HF, heart failure; HfPEF, heart failure with preserved ejection fraction; IHM, implantable haemodynamic monitor; I-V, inverse variance; LAPTOP-HF, Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy; REDUCE-HF, Reducing Events in Patients with Chronic Heart Failure.

treatment had a 28% relative reduction in total worsening HF events. In the random-effects model, the average reduction was similar, but the CIs were wide, encompassing a potential 68% reduction to a 14% increase in such events with IHM-guided care. The difference in significance levels between models is in keeping with the high heterogeneity in the pooled sample. The effectiveness of IHM-guided treatment in patients with HfPEF remains uncertain and further trials are required with analyses in this population pre-specified in the study designs. On the available evidence, the patients who might benefit the most from IHM would have several characteristics, including a history of volume overload (as indicated by a recent HF hospitalisation), persisting symptoms and an EF of <50%.

This analysis has limitations. First, only two trials examined an IHM that is currently available (CardioMEMS), and three IHMs were examined over 18 years of investigation during which time the background management of patients with HF evolved with advancements in drug and device therapies.24 25 28–30 Each IHM measured a different haemodynamic parameter. However, the IHM’s haemodynamic measures were physiologically related (eg, ePAD (COMPASS-HF) provided a surrogate estimate for left atrial pressure (LAPTOP-HF)). Potential sources of bias exist. REDUCE-HF was terminated following concerns regarding 4-year pressure sensor failure in patients from other Chronicle device studies. A total of 400 patients from a recruitment target of 1300 patients had enrolled at the point of study termination. Consequently, REDUCE-HF was underpowered, with only 181 events reported compared with the 648 events expected. LAPTOP-HF was also terminated early after 1 year due to periprocedural safety concerns,11 and mortality data from this trial were not available. The meta-analysis effect estimates may have changed had both the REDUCE-HF and LAPTOP-HF trials achieved target recruitment. However, the inclusion of these studies in the meta-analysis reduced selection bias by including at least 1 year of follow-up data on clinically relevant outcomes from these RCTs. Based on patients in REDUCE-HF and LAPTOP-HF having a mean EF of 23%±7% and 30%±15%, respectively, both trials were included in the HFrEF analysis. The initial REDUCE-HF inclusion criteria also required participants to have an implantable cardioverter–defibrillator (ICD), favouring recruitment from a population with more severe HFrEF, the patient group in whom ICD implantation predominates. We cannot, however, completely exclude the possibility that some patients had EFs above these ranges. Individual cohort numbers were not available from all studies for all EF groups. We did not have individual participant level data to test the interaction between EF and IHM-guided care.

CONCLUSIONS
IHM-guided treatment reduced total HF hospitalisation and worsening HF events. In subgroup analyses, patients with HFrEF appear to benefit from IHM-guided care, but whether the same benefit is present in patients with HfPEF remains uncertain. Further trials with pre-specified analyses of patients with an EF of ≥50% are required.

Contributors JPC conceived and designed the study, extracted the data, performed the analyses and contributed to the writing of the manuscript. MMYL extracted the data, performed the analyses and contributed to the writing of the manuscript. JJVM, RSG and MCP contributed to the writing of the manuscript. PSJ conceived and...
designed the study, contributed to the writing of the manuscript and is the guarantor of this study.

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Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. All five trials included in this meta-analysis were approved by a local ethics committee at each of the participating trials sites and complied with the Declaration of Helsinki. The participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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REFERENCES


